Risk Management Plan

EUROPEAN UNION RISK MANAGEMENT PLAN

FEZOLINETANT (VEOZA™)

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European Union Risk Management Plan for Fezolinetant

RMP version to be assessed as part of this application:

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The rationale for submitting an updated RMP: This risk management plan (RMP) has been updated to revise the milestones for the additional pharmacovigilance activity: non-interventional post-authorization safety study (NI-PASS) evaluating the effectiveness of risk minimization measures (RMMs) for the important identified risk of "Drug-induced liver injury (DILI)".

Summary of significant changes in this RMP:

- Updated the milestones for the additional pharmacovigilance NI-PASS study in Table Part III.1of the RMP.

Other RMP versions under evaluation:

RMP Version Number(s)	Submitted on	Procedure Number(s)
Not applicable	Not applicable	Not applicable

Details of the currently approved RMP:

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List of Abbreviations

Abbreviation	Definition
ADR	Adverse Drug Reaction
AESIs	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLOSER	Clarifying Vaginal Atrophy's Impact on Sex and Relationships
CNS	Central Nervous System
C-SSRS	Columbia Suicide Severity Rating Scale
CTD	Common Technical Document
CYP 1A2	Cytochrome P450 1A2
DBL	Direct Bilirubin
DDI	Drug-Drug Interaction
DHPC	Direct Healthcare Professional Communication
DILI	Drug-Induced Liver Injury
ECG	Electrocardiogram
EEA	European Economic Area
EEG	Electroencephalogram
eGFR	Estimated Glomerular Filtration Rate
EHR	Electronic Health Record
EMA (EMEA)	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FMP	Final Menstrual Period
GVP	Guideline on Good Pharmacovigilance Practices
HCP	Healthcare Professional
hERG	the human Ether-à-go-go-Related Gene
HRT	Hormonal Replacement Therapy
HT	Hormone therapy
IC	Inhibitory Concentration
ICH	International Conference on Harmonization
INN	International Nonproprietary Name
INR	International Normalized Ratio
KNDy	Kisspeptin/Neurokinin B/Dynorphin
LFT	Liver Function Test
LSMP	Liver Safety Monitoring Panel
LVP	Left Ventricular Pressure
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MRHD	Maximum Recommended Human Dose
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis

Abbreviation	Definition
NI-PASS	Non-Interventional Post-Authorization Safety Study
NK	Neurokinin
NKB	Neurokinin B
NOAEL	No Observed Adverse Effect Level
PBRER	Periodic Benefit-Risk Evaluation Report
PRAC	Pharmacovigilance Risk Assessment Committee
POP	Population
RMM	Risk Minimization Measure
RMP	Risk Management Plan
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA (Medical Dictionary for Regulatory Activities) Queries
SNRIs	Serotonin Noradrenaline Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
SSNRIs	Selective Serotonin-Norepinephrine Reuptake Inhibitors
TBL	Total Bilirubin
SWAN	Study of Women's Health Across the Nation
TEAE	Treatment-Emergent Adverse Events
TQT	Thorough QT/QTc
TVU	TransVaginal Ultrasound
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VMS	Vasomotor Symptoms

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PART I: PRODUCT(S) OVERVIEW

Data-lock point for this Module	21 Jan 2022
Version when Module last updated	4.0

Table Part I.1: Product Overview

Active substance {International Nonproprietary Name [INN] or common name}	Fezolinetant
Pharmacotherapeutic group(s) Anatomical Therapeutic Classification (ATC) Code	Other gynecologicals G02CX06
Marketing Authorization Holder	Astellas Pharma Europe B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	VEOZA™
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class Selective neurokinin 3 (NK3) receptor antagonist
	Summary of mode of action Fezolinetant is a nonhormonal selective neurokinin 3 (NK3) receptor antagonist. It blocks neurokinin B (NKB) binding on the kisspeptin/neurokinin B/dynorphin (KNDy) neuron, which is postulated to restore the balance in KNDy neuronal activity in the thermoregulatory center of the hypothalamus.
	Important information about its composition Chemical name: (4-fluorophenyl) [(8R)-8-methyl-3-(3-methyl-1,2,4- thiadiazol-5-yl)-5,6-dihydro [1,2,4] triazolo[4,3-a] pyrazin-7(8H)-yl] methanone Molecular Formula: $C_{16}H_{15}FN_6OS$ Molecular Weight: 358.39.
Hyperlink to the product information	[Module 1.3.1]
Indication(s) in the EEA	Current: Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose is 45 mg once daily.

	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 45 mg film-coated tablet
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC: Anatomical Therapeutic Classification; EEA: European Economic Area; EU: European Union; INN: International Nonproprietary Name; KNDy: kisspeptin/neurokinin B/dynorphin; NK: Neurokinin; NKB: Neurokinin B; RMP: Risk Management Plan; VMS: Vasomotor Symptoms

PART II: SAFETY SPECIFICATION

PART II: MODULE SI. EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

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VMS associated with menopause:

Fezolinetant is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause. During the menopausal transition, physical and psychological symptoms may be experienced among more than 80% of women [Constantine et al, 2016; Minkin et al, 2015; Hunter et al, 2012; Williams et al, 2008]. The average age of menopause is approximately 50 years, but the transition may begin in a woman's early 40s and may stretch into her 70s [Constantine et al, 2016; Rödström et al, 2002]. The incidence, prevalence, frequency, and severity of the most common menopausal symptoms (VMS) may vary with a woman's menopausal transition stage, age, race/ethnicity, and geography, along with the study population, research methodology, and symptom definitions [Avis et al, 2018; Islam et al, 2017; Freeman et al, 2011].

Incidence:

The majority of published studies on VMS associated with menopause have evaluated the prevalence of the condition as opposed to the incidence. The incidence can range widely taking into account the study subjects' initial age when entering into a study and menopausal transition status along with the length of the study follow-up [van den Berg et al, 2015; Freeman et al, 2009]. However, no direct estimate of the incidence of VMS has been publicly reported.

Prevalence:

Global data

Worldwide, most women aged 40-64 years have reported VMS, with an average prevalence of 57% globally as summarized in an extensive review [Makara-Studzińska et al, 2014]. From the global Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) survey project, the prevalence of VMS and other menopausal symptoms were assessed among postmenopausal women 55-65 years-old in the United States (US), Canada, and 7 European countries [Minkin et al, 2015]. Overall, hot flashes had been experienced in 72% and night sweats in 62% of the women. The prevalence of hot flashes ranged from 73% (US) to 78% (Canada) in North America, and in Europe from 65% in Sweden and Denmark, to 68% in Italy, 70% in Norway and Finland, 72% in France, and up to 80% in Great Britain. For night sweats, the prevalence was lowest in Italy at 41% and increased up to 72% in Great Britain [Minkin et al, 2015].

European Data

Some studies have researched VMS across various European countries where the prevalence has ranged from 50% to 85% among middle-aged to elderly women. A menopausal symptom survey conducted among women over age 45 in France, Germany, Italy, Spain, and the United Kingdom (UK) revealed that hot flashes were the most prevalent menopausal symptom at 85% (range: 82% – 89%) while night sweats occurred among 57%-67% in 4 countries and were higher in the UK (75%) [Constantine et al, 2016]. Hot flashes tended to have the highest prevalence in the 45-54-year age group and declined slightly after age 65 where approximately 25%-57% of the subjects still suffered from hot flashes and 10% - 44% from night sweats. The National Health and Wellness Survey was another study conducted across multiple European countries (France, Germany, Italy, Spain, UK). They included postmenopausal women 40-75 years-old and reported that 50.3% were currently enduring VMS (mild: 24.6%, moderate: 17.6%, severe: 8.1%) [Dibonaventura et al, 2013].

Prevalence by severity

While VMS severity was defined in clinical studies and some observational studies based on the 2005 European Medicines Agency Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women [EMA, 2005], there were various definitions applied in other observational studies, which makes comparison across studies difficult. The prevalence of moderate to severe VMS in postmenopausal women has been found to vary by geographic region, with 34% in the US, 40% in Europe, and 16% in Japan, as reported in a global survey among women aged 40-65 years [Nappi et al, 2021]. The peak prevalence of moderate to severe VMS in postmenopausal women in the US was 46% occurring in the first 2 years after the final menstrual period [Freeman et al, 2014]. A study conducted across multiple European countries and restricted to postmenopausal women (aged 40-75 years) reported that 24.6% of the participants had mild VMS, 17.6% had moderate VMS and 8.1% had severe VMS [Dionaventura et al, 2013]. In the US, a study reported that among women aged 60 years or older, 41.2% reported moderate to severe VMS [David et al, 2018]. In Latin America, severe VMS has been reported to occur in 10.8% of perimenopausal women, 12.3% of women in early menopause, and 11.5% of women in late menopause [Blümel et al, 2011].

Demographics of the population in the proposed indication – age, racial and/or ethnic origin, and risk factors for the disease:

VMS are associated with age where the prevalence tends to peak among women aged 45-54 years and decline slightly after the age of 55 years. For example, Gartoulla et al. reported that the prevalence of moderate to severe VMS was 2.8% in premenopausal women, 28.5% in postmenopausal women younger than 55 years, 15.1% in postmenopausal women aged 55-59 years, and 6.5% in postmenopausal women aged 60-65 years [Gartoulla et al, 2015].

African American women are most likely to report VMS, followed by Hispanic, Caucasian, and Chinese/Japanese women in descending order [Thurston and Joffe, 2011; Simpkins et al,

2009; Freeman and Sherif, 2007]. For example, longitudinal data from the US multi-racial/ethnic Study of Women's Health Across the Nation (SWAN) show that a higher percentage of African American women reported frequent VMS across all stages of the menopausal transition compared with other racial/ethnic groups [Gold et al, 2006]. In the transition from late perimenopause to post menopause, approximately 80% of African American women reported any hot flashes compared with about 70% of white women.

Many factors are associated with an increased risk of VMS. These include transition to late perimenopausal status, change in reproductive hormone levels, current smoking, obesity/increased body mass index, lower educational attainment, anxiety, depression, history of migraine and genetic background [Maleki et al, 2019; Avis et al, 2015; Gallicchio et al, 2015; Freeman et al, 2014; Hunter et al, 2012; Thurston and Joffe, 2011; Ziv-Gal and Flaws, 2010].

Main existing treatment options:

Hormone therapy (HT) (also commonly referred to as hormone replacement therapy) is the most effective treatment of the relief of VMS for most menopausal women [EMAS, 2022; NAMS Position Statement, 2023]. HT works by supplementing the decreasing production of hormones by the ovaries [Martin and Barbieri, 2022a]; the key component of HT is estrogen, often combined with progesterone analog to reduce the excess risk of endometrial hyperplasia and carcinoma with estrogen-only therapy [Martin and Barbieri, 2022a; Martin and Barbieri, 2022b]. HT has several limitations associated with serious health risks. It is associated with an increased risk of depression, cardiovascular disease, breast cancer, stroke, deep vein thrombosis, and pulmonary embolism [Martin & Rosenson, 2021; Shea et al, 2020; Collaborative Group on Hormonal Factors in Breast Cancer, 2019; De et al, 2010; Rossouw et al, 2002]. These safety findings limit the populations who are appropriate candidates for HT based on benefit-risk considerations.

There are nonhormonal therapies for VMS available. Selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), gabapentin, and clonidine have been shown to improve VMS associated with menopause in clinical trials, although to a lesser extent than HT [Baber et al, 2016; ACOG Clinical Management Guidelines, 2014]. The European Menopause and Andropause Society suggests the following for those who do not wish to initiate HT or who are not eligible for it in their consensus statement: SSRIs and selective serotonin-norepinephrine reuptake Inhibitors (SSNRIs); gabapentin and pregabalin; clonidine and oxybutynin. Each of these alternatives has the following limitations, respectively: caution is advised for women with breast cancer treated with tamoxifen; concerns misuse and dependence moderate effectiveness; side-effects such as the higher risk of dementia [EMAS, 2022].

Widely employed as over the counter remedies, natural remedies including herbal/non-prescription products have not been approved for VMS treatment and their safety and efficacy are not well established [EMAS, 2022; NAMS Position Statement, 2022; Baber et al, 2016; de Villiers et al, 2016; Stuenkel et al, 2015; ACOG Clinical Management Guidelines, 2014; SOGC Clinical Practice Guideline: Managing Menopause, 2014].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The reported duration of VMS associated with menopause varies by studies. In the US SWAN study, frequent VMS lasted for a median of 7.4 years during the menopausal transition and persisted for 4.5 years after the final menstrual period (FMP) [Avis et al, 2015].

The presence of VMS was associated with a lower quality of life [Utian et al, 2005]. Among postmenopausal women, VMS interfered with daily activities, mostly sleep, mood, concentration, energy level, and overall quality of life, and to a lesser extent with work, social, leisure, and sexual activities [Kim et al, 2018; Katon et al, 2016; Williams et al, 2009]. Significant increases in work and activity impairment with increasing VMS severity have been reported and increasing VMS severity has been associated with lower levels of health status [Whitely et al, 2013]. Furthermore, some observational studies found an association between menopausal symptoms including VMS, and cardiovascular disease risk including coronary heart disease and stroke, although causality is not established [NAMS Position Statement 2022; Thurston et al, 2021; AHA statement 2020; Muka et al, 2016; Szmuilowicz et al, 2011].

Important Co.-morbidities:

In addition to VMS associated with menopause, there are several Co.-morbid conditions that are common within this population, further complicating the management of VMS and treatment decision-making. These include diabetes, hypertension, dyslipidemia, metabolic syndrome, non-alcoholic fatty liver disease, fracture, sleep disorders, and migraine [Mulvagh et al, 2021; DiStefano et al, 2020; Slopien et al, 2018; CDC NCHS 2015; Franco et al, 2015; Hernlund et al, 2013; Joffe et al, 2010].

PART II: MODULE SII. NONCLINICAL PART OF THE SAFETY SPECIFICATION

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Key safety findings from nonclinical studies	
Key safety findings (from nonclinical studies)	**Relevance to human usage**
Toxicity findings include:	
Acute & repeat-dose toxicity	
Hematolymphoid system Thrombocytopenia occurred in cynomolgus monkeys at high systemic exposures relative to human exposure (61-fold the human AUC_{24} at the MRHD) and was reversible with a withdrawal period.	Hematolymphoid system In phase 3 clinical trials, laboratory assessments of thrombocytopenia and the incidences of treatment-emergent AESIs of thrombocytopenia showed no clinically relevant differences across treatment groups. The reported events of thrombocytopenia were consistent with that observed in the background epidemiology for this population. The AUC_{24} at the NOAEL of fezolinetant in cynomolgus monkeys (25 mg/kg per day) was 43-fold the human AUC_{24} at the MRHD, thus there is little hematologic risk to individuals at the clinically relevant doses.
Liver In all rat repeated-dose toxicity studies, increased liver weight and centrilobular hepatocellular hypertrophy were observed at ≥ 100 mg /kg per day (≥ 143-fold the human AUC_{24} at the MRHD). These findings are considered adaptive changes related to the induction of hepatic metabolic enzymes. Similar changes were not observed in cynomolgus monkeys.	Liver Liver findings are considered to be a rat specific effect secondary to the induction of hepatocyte metabolic enzymes and, therefore, do not constitute a clinical risk.
Thyroid In all rat toxicity studies, thyroid follicular cell hypertrophy was observed at ≥ 100 mg /kg per day (≥ 143-fold the human AUC_{24} at the MRHD). This change was considered related to adaptive changes in the liver correlated with hepatic enzyme induction in rats. Similar changes were not observed in cynomolgus monkeys.	Thyroid Thyroid findings are considered to be a rat specific effect secondary to the induction of hepatocyte metabolic enzymes and, therefore, do not constitute a clinical risk.
Female reproductive organs In female rats, daily administration of fezolinetant for 26 weeks at doses equal to or greater than	Female reproductive organs Considering that fezolinetant is indicated for the treatment of VMS associated with

Key safety findings from nonclinical studies	
Key safety findings (from nonclinical studies)	**Relevance to human usage**
30 mg/kg/day (56-fold the human AUC_{24} at the MRHD) showed uterine atrophy and epithelial mucification of the vagina and cervix. In female cynomolgus monkeys, daily administration for 39 weeks at doses equal to or greater than 10 mg/kg/day (26-fold the human AUC_{24} at the MRHD) showed reduced ovarian activity. These findings were reversible.	menopause, the effects on female reproductive organs are not considered to be serious clinical problems.
Reproductive and Developmental toxicity	
Fezolinetant had no effect on female fertility up to 100 mg/kg/day in rats (143-fold the human AUC_{24} at the MRHD). Fezolinetant had no effect on early embryonic development up to 100 mg/kg/day in rats (143-fold the human AUC_{24} at the MRHD). In embryo-fetal development toxicity studies, embryo-lethality was noted at an AUC_{24} 128- and 174-fold higher than the human AUC_{24} at the MRHD in rats and rabbits, respectively. Rabbits also showed increased late resorption and reduced fetal weight were observed at 75 mg/kg/day (28-fold the human AUC_{24} at the MRHD). The no observed adverse effect level (NOAEL) for embryo-fetal development was 50 mg/kg/day in rats and 45 mg/kg/day in rabbits (62- and 16-fold the human AUC_{24} at the MRHD in rats and rabbits, respectively). Fezolinetant did not show teratogenic potential in either rats or rabbits. In the pre- and post-natal development study in rats, the NOAEL for maternal and fetal toxicity was 30 mg/kg/day (36-fold the human AUC_{24} at the MRHD) based on delayed parturition and embryo-lethality at 100 mg/kg/day. The NOAEL for F1 generation development was determined to be 100 mg/kg/day for females (204-fold the human AUC_{24} at the MRHD) and 10 mg/kg/day for males (11-fold the human AUC_{24} at the MRHD). The F1 male showed incomplete balanopreputial separation which may delay male reproductive maturation or affect fertility.	There is no data on the effect of fezolinetant on human fertility. Considering that fezolinetant is indicated for the treatment of VMS associated with menopause, it is unlikely that fertility would be affected. The use of fezolinetant is contraindicated during pregnancy and is not indicated during lactation. Considering that fezolinetant is indicated for the treatment of VMS associated with menopause, it is unlikely that a pregnant or breast-feeding woman or their child/fetus would be affected. At high systemic exposure that are unlikely to be achieved at clinically relevant doses, fezolinetant has the potential to cause embryo loss.
Genotoxicity	
Fezolinetant and the major metabolite showed no genotoxic potential in the bacterial reverse mutation test, chromosomal aberration test, or in vivo micronucleus test.	Not applicable

Key safety findings from nonclinical studies	
Key safety findings (from nonclinical studies)	**Relevance to human usage**
Carcinogenicity	
An increase in the incidence of thyroid follicular cell adenoma at 100 mg/kg per day was noted in a 2-year rat carcinogenicity study (doses of 10, 30, and 100 mg/kg per day). In the 26-week carcinogenicity study in rasH2 transgenic mice (doses of 50, 150 and 450 mg/kg per day), neoplasms were not induced.	The increase in the incidence of thyroid follicular cell adenoma (benign) is considered to be a rat specific effect secondary to the induction of hepatocyte metabolic enzymes and, therefore, does not constitute a clinical carcinogenic risk.
General safety pharmacology findings:	
Cardiovascular (including potential for QT interval prolongation)	
In the hERG assay, fezolinetant inhibited the potassium current in a dose related manner and an IC_{50} value of 231.8 µmol/L was determined (371-fold the human $C_{max,u}$ at 45 mg). In the telemetry study in cynomolgus monkeys, there were no significant effects on any parameters up to 50 mg/kg (59-fold the human C_{max} at 45 mg). Although there was a trend toward decreases in the mean maximal rate of rise of LVP ($+dP/dt_{max}$), and systolic and mean arterial blood pressure (with a slight increase in heart rate), these changes were not considered to indicate serious effects on the cardiovascular system because they were slight and without statistical significance. The safety pharmacology studies indicate that fezolinetant has little or no cardiovascular effects.	In phase 3 clinical trials, there were no clinically relevant changes in the quantitative interval measures of the ECG parameters in any of the treatment groups in the 12-week safety populations and in the 52-week safety populations. An evaluation of the safety database of fezolinetant phase 3 studies of TEAEs related to cardiovascular health showed no events of ventricular fibrillation, ventricular tachycardia, electrocardiogram T wave abnormal, QT prolongation nor the events of Torsades de pointes. A model based TQT study waiver package is included in the MAA dossier. No dedicated clinical TQT study was deemed necessary. The model predicted upper 90% CI for ddQTcF did not exceed 10 msec at the therapeutic concentration, supratherapeutic concentration, or 10-times the therapeutic concentration indicating a lack of QT prolongation potential for fezolinetant at the clinical dosage regimen. In line with ICH E14 recommendations and the Scientific White Paper on Concentration QTc Modeling [Garnett et al, 2018].
Nervous system	
In the rat safety pharmacology study, constricted pupils, decreased activity, touch escape response, and grip strength, which are considered to be indicative of sedation, were noted. The NOAEL for sedation-like effects was 30 mg/kg/day and 60-fold the human C_{max} at the MRHD. The CNS findings were not observed in cynomolgus monkeys. Taken together, these nonclinical data indicate that fezolinetant poses little CNS risk to patients at the MRHD.	In the clinical program, there is no evidence to support a risk for depression, wakefulness, or memory loss in individuals with VMS treated with fezolinetant. Insomnia is considered to be an ADR for fezolinetant. There was no effect of fezolinetant on suicidal ideation or behavior as assessed by C-SSRS or TEAEs. The clinical data show no evidence of abuse liability potential with fezolinetant. There is no indication that fezolinetant affects the ability to drive or

Key safety findings from nonclinical studies	
Key safety findings (from nonclinical studies)	**Relevance to human usage**
	operate machinery.

ADR: Adverse Drug Reaction; AESIs: Adverse Events of Special Interest; AUC: Area Under Curve; CNS: Central Nervous System; CI: Confidence Interval; C-SSRS: Columbia Suicide Severity Rating Scale; ECG: Electrocardiogram; hERG: The human Ether-à-go-go-Related Gene; IC: Inhibitory Concentration; ICH: International Conference on Harmonization; LVP: Left Ventricular Pressure; MAA: Marketing Authorization Application; MRHD: Maximum Recommended Human Dose; NOAEL: No Observed Adverse Effect Level; TEAE: Treatment-Emergent Adverse Events; TQT: Thorough QT/QTc; VMS: Vasomotor Symptoms.

PART II: MODULE SIII. CLINICAL TRIAL EXPOSURE

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In completed studies of the fezolinetant clinical development program, 3643 subjects have been exposed to fezolinetant cumulatively of whom 3314 with VMS. The presentations below provide the cumulative exposure and the exposure in VMS, followed by the exposures in the subgroups. Completed studies include ESN364-UF-02, 2693-CL-0006, 2693-CL-0007, 2693-CL-0008, 2693-CL-0009, 2693-CL-0010, 2693-CL-0012, 2693-CL-0020, 2693-CL-0030, ESN364-CPK-101, ESN364-CPK-102, ESN364-CPK-103, ESN364-PCO-201, ESN364-HF-204, 2693-CL-0205, 2693-CL-0206, 2693-CL-0301, 2693-CL-0302, 2693-CL-0304, 2693-CL-0305, 2693-CL-0307, and 2693-CL-0312.

Table SIII.1: Duration of exposure

Cumulative for all indications		
Duration of exposure	**Subjects**	**Person years**
<1 month	429	10.35
1 to <3 months	718	149.89
3 to <6 months	570	232.43
≥ 6 months	1926	1829.26
Total	**3643**	**2221.94**
VMS		
Duration of exposure	**Subjects**	**Person years**
<1 month	156	6.41
1 to <3 months	663	137.46
3 to <6 months	569	232.18
≥ 6 months	1926	1829.26
Total for indication	**3314**	**2205.31**

VMS: vasomotor symptoms; Subject-Year of Exposure is calculated by total duration of exposure/365.25.

Table SIII.2: Exposure by age group and gender

All Indications				
	Subjects		**Person years**	
Age group	**M**	**F**	**M**	**F**
Adults (18 to 64 years)	63	3523	1.00	2192.14
18 to <40 years	50	116	0.76	11.84
40 to <55 years	13	1767	0.24	1114.05
55 to <65 years	0	1640	0	1066.25
Elderly (65-74 years)	0	57	0	28.80
Total	**63**	**3580**	**1.00**	**2220.94**

VMS				
	Subjects		**Person years**	
Age group	**M**	**F**	**M**	**F**
Adults (18 to 64 years)	n/a	3277	n/a	2176.57
18 to <40 years	n/a	0	n/a	0
40 to <55 years	n/a	1697	n/a	1110.66
55 to <65 years	n/a	1580	n/a	1065.91
Elderly (65-74 years)	n/a	37	n/a	28.74
Total	**n/a**	**3314**	**n/a**	**2205.31**

F: female; M: male.; n/a: not applicable; VMS: vasomotor symptoms; Subject-Year of Exposure is calculated by the total duration of exposure/365.25.

Table SIII.3: Exposure by daily dose

VMS		
Dose of exposure	**Subjects**	**Person years**
15 mg	53	12.31
30 mg	1671	1128.44
45 mg	1326	1009.45
>= 60 mg	264	55.11
Total	**3314**	**2205.31**

mg: milligram; VMS: vasomotor symptoms; Subject-Year of Exposure is calculated by total duration of exposure/365.25.

Table SIII.4: Exposure by ethnic origin

VMS		
Ethnic origin	**Subjects**	**Person years**
White	2246	1589.32
Black or African American	473	334.22
Asian	566	261.58
Other	26	18.17
Unknown	3	2.03
Total	**3314**	**2205.31**

VMS: vasomotor symptoms; Subject-Year of Exposure is calculated by total duration of exposure/365.25.

PART II: MODULE SIV. POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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SIV.1 Exclusion criteria in phase 3 clinical trials within the development program

The phase 3 studies in the clinical development program for VMS associated with menopause comparing fezolinetant to placebo initially included studies 2693-CL-0301, 2693-CL-0302 and 2693-CL-0304. Subsequently, phase 2 and phase 3 studies 2693-CL-0305, 2693-CL-0307, 2693-CL-0206 and 2693-CL-0312 were completed. The exclusion criteria for these 7 studies were generally similar and are described in the below Table SIV.1.

Table SIV.1: Important exclusion criteria in phase 2 and 3 clinical trials across the development program

Criterion 1	**Subject uses a prohibited therapy (strong or moderate CYP1A2 inhibitors, HRT, hormonal contraceptive, any treatment for VMS [prescription, over the counter, or herbal]) or is not willing to wash out and discontinue such drugs for the full extent of the study.**
Reason for being an exclusion criterion	Strong or moderate CYP1A2 inhibitors Co-administration with fezolinetant was excluded as it leads to increased AUC as confirmed in a dedicated phase 1 drug interaction study (2693-CL-0006). HRT, hormonal contraceptive, any treatment for VMS Co-administration with fezolinetant was excluded to avoid factors that could have confounded a complete understanding of the efficacy data of fezolinetant and ensure interpretability of the data.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	Strong or moderate CYP1A2 inhibitors The proposed SmPC instructs to avoid concomitant use of moderate or strong CYP1A2 inhibitors with VEOZA and therefore this is not considered missing information. HRT, hormonal contraceptive, any treatment for VMS Hormonal contraceptives which contain ethinyl estradiol are considered as a moderate CYP1A2 inhibitors, thus the risk of pharmacokinetic DDI cannot be excluded. Ethinylestradiol containing contraceptive is contraindicated. HRT is known as a weak CYP1A2 inhibitor. Since the clinical impact by CYP1A2 weak inhibitors considered to be low, the risk of pharmacokinetics DDI with HRT is considered to be low.

	Of note: other medicine that in theory could be used as therapy for moderate to severe VMS but was used during the clinical trials for other indications (such as SSRI for depression) were not an exclusion criterion in the clinical trials if women were on a stable dose for the treatment of depression and not VMS. There is no scientific rationale to suspect a safety profile for concomitant use of these treatments which is different from what has been characterized thus far and therefore this is not considered missing information.
Criterion 2	**Subject has a known substance abuse or alcohol addiction within 6 months of screening, as assessed by the investigator.**
Reason for being an exclusion criterion	Fezolinetant can cross the blood brain barrier. Pre-existing conditions related to abuse or addiction could have interfered with the assessment of efficacy and/or safety in the clinical trials.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	In the phase 3 program, there were no effects of fezolinetant on the CNS (with the possible exception of insomnia, which is considered an ADR). Also, there was no evidence of abuse liability potential. This is supported by the results from the phase 2b and nonclinical trials. In the phase 2b study, 1 TEAE of Euphoric mood was reported, that resolved spontaneously on treatment. The nonclinical data showed sedation like-CNS findings in rats at exposures higher than MRHD and no withdrawal syndrome or reinforcing effects were induced. No CNS findings were observed in cynomolgus monkeys. The data support the CNS safety of fezolinetant. Because of the absence of scientific rationale to suspect a different safety profile in the population described in the exclusion criterion, this exclusion criterion is not considered missing information.
Criterion 3	**Subject has a previous or current history of a malignant tumor, except for basal cell carcinoma.**
Reason for being an exclusion criterion	Malignancy or its treatment could have interfered with the evaluation of efficacy and/or safety and to ensure interpretability of the data.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	An in-depth review of reported events of malignant neoplasm did not indicate fezolinetant-related risk, generally, or for specific malignancies. The events observed in the fezolinetant development program were consistent with the types of malignancies commonly noted in the target study population [Ferlay et al, 2021, SEER*Explorer, 2015-2019]. The absence of drug effect was supported by the short time to awareness in the majority of cases and alternative etiologies such as a pre-existing condition at study entry, along with prior history and/or risk factors for the events. There was no known agent that could be singularly responsible for the infrequent and diverse pathophysiologies of malignancy in the fezolinetant program.

	This is supported by nonclinical data and literature. There was no evidence of genotoxicity or carcinogenicity in the fezolinetant nonclinical program. The literature does not suggest a plausible mechanistic hypothesis for the role of NK3 receptor antagonism in the development of neoplasms. On the contrary, tachykinin antagonism is a plausible therapeutic antineoplastic target [Munoz and Covenas, 2014]. There is no evidence of a risk of malignancy with fezolinetant in the clinical trial program and fezolinetant has not been found to be carcinogenic based on nonclinical data. Also, there is no scientific rationale to suspect a different safety profile in the population described in the exclusion criterion. Use in patients described in this exclusion criterion is not considered relevant as missing information.
Criterion 4	**Subject has an unacceptable result from the TVU assessment at screening, i.e., the full length of endometrial cavity cannot be visualized or the presence of a clinically significant finding.**
Reason for being an exclusion criterion	A TVU assessment at screening was necessary to assess endometrial health in the phase 3 program in women with a uterus. Endometrial health was a safety objective as there are NK3 receptors in the reproductive tract and because it complies with EMA and FDA guidance for the evaluation of products for the treatment of menopausal symptoms in this indication. An unacceptable result at screening could have interfered with the assessment of safety in the clinical trials.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	In the phase 3 program fezolinetant had no impact on endometrial thickness after 1 year of treatment in women with a uterus. This is supported by phase 2 and nonclinical findings. In the phase 2b study, there was no increase in endometrial thickness compared with placebo. In repeated-dose toxicities studies, there were no abnormal thickenings of the endometrium in the sexually matured cynomolgus monkey. Also, mechanistically, fezolinetant is not expected to change estrogen levels in postmenopausal women. The data support the endometrial safety of fezolinetant. Because of the absence of scientific rationale to suspect a different safety profile in the population described in the exclusion criterion, this exclusion criterion is not considered missing information.
Criterion 5	**Subject has an endometrial biopsy confirming presence of disordered proliferative endometrium, endometrial hyperplasia, endometrial cancer, or other clinically significant findings in the opinion of the investigator at screening.**
Reason for being an exclusion criterion	A biopsy was necessary to assess endometrial health in the phase 3 program in women with a uterus. Endometrial health was a safety objective as there are NK3 receptors in the reproductive tract and because it complies with EMA and FDA guidance for the evaluation of products for the treatment of menopausal symptoms. A biopsy

	with a clinically significant finding could have interfered with the assessment of safety in the clinical trials.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	In the phase 3 studies in women with a uterus, there was no association between fezolinetant exposure and risk of endometrial hyperplasia or malignancy. The FDA pre-specified criterion of ≤ 1% with the upper bound of the one-sided 95% CI ≤4% was met. This is supported by phase 2b data that had no reports of clinically significant endometrial biopsy finding or endometrial hyperplasia. The data support the endometrial safety of fezolinetant. Because of the absence of scientific rationale to suspect a different safety profile in the population described in the exclusion criterion, this exclusion criterion is not considered missing information. This exclusion criterion was removed from the latest completed study 2693-CL-0312 and 2693-CL-0206 based on the data from previous studies and reducing the burden of the procedure to the patients.
Criterion 6	**Subject has a history within the last 6 months of undiagnosed uterine bleeding.**
Reason for being an exclusion criterion	Endometrial health was a safety objective as there are NK3 receptors in the reproductive tract and because it complies with EMA and FDA guidance for the evaluation of products for the treatment of menopausal symptoms. If the cause of uterine bleeding was diagnosed (e.g., endometriosis, polyp, etc.) and not otherwise excluded, this exclusion criterion did not apply. A uterine bleeding with an unknown diagnosis could have interfered with the assessment of safety in the clinical trials and was excluded.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	In the phase 3 program, the incidence of the TEAE of uterine bleeding was low. This is supported by the findings of phase 2 studies, with no events of uterine bleeding in phase 2a in the fezolinetant group, and a few isolated cases in phase 2b, which were not associated with clinically significant endometrial biopsy findings. The data support the endometrial safety of fezolinetant. Because of the absence of scientific rationale to suspect a different safety profile in the population described in the exclusion criterion, this exclusion criterion is not considered missing information.
Criterion 7	**Subject has a history of seizures or other convulsive disorders.**
Reason for being an exclusion criterion	Fezolinetant can cross the blood brain barrier. Pre-existing conditions related to seizures or other convulsive disorders could have interfered with the assessment of efficacy and / or safety in the clinical trials. In addition, in the 3-month toxicology study in rats, convulsive episodes were reported. An independent assessment concluded that

	this was not linked to fezolinetant but rather a stress-and-fear reaction (expert report from Brunner Naga Health Science Consulting, Switzerland). Nevertheless, seizures and convulsive disorders were considered events to be closely monitored during the phase 3 program and no seizures or EEG abnormalities were reported.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	In the phase 3 program, there were no effects of fezolinetant on the CNS (with the possible exception of insomnia, which is considered an ADR). This is supported by results from phase 2, phase 1, and pre-clinical studies. In phase 2, phase 1 studies, and in 3-month and 9-month toxicology studies in non-human primates, no signs of convulsive activity were observed. In a long-term CNS toxicity study in rats no seizures were detected based on review of video-EEG records. In addition, no convulsions were observed in a subsequent 6-month study in rats. The data support the CNS safety of fezolinetant. Because of the absence of scientific rationale to suspect a different safety profile in the population described in the exclusion criterion, this exclusion criterion is not considered missing information.
Criterion 8	**Subject has a medical condition or chronic disease (including history of neurological [including cognitive], hepatic, renal, cardiovascular, gastrointestinal, pulmonary [e.g., moderate asthma], endocrine or gynecological disease) or malignancy that could confound the interpretation of the study outcome in the opinion of the investigator.**
Reason for being an exclusion criterion	Subjects were excluded in order to avoid factors that could have confounded a complete understanding of the safety and efficacy data of fezolinetant used in patients with VMS and ensure interpretability of the data.
Is it considered to be included as missing information?	Yes: use in patients with chronic hepatic impairment (Child Pugh B and C).
Rationale (if not included as missing information)	Based on nonclinical and clinical findings, no safety concerns are suspected, with the exception of chronic hepatic impairment (Child Pugh B and C) patients, based on nonclinical data and phase 1 data (2693-CL-0007), Section SVII 3.2.
Criterion 9	**Subject has active liver disease, jaundice, elevated liver aminotransferases (ALT or AST), elevated total or direct bilirubin (DBL), elevated International Normalized Ratio (INR), or elevated alkaline phosphatase (ALP). Patients with mildly elevated ALT or AST up to 1.5 times the upper limit of normal (ULN) can be enrolled if total and DBL are normal. Patients with mildly elevated ALP (up to 1.5 × ULN) can be enrolled if cholestatic liver disease is excluded and no cause other than fatty liver is diagnosed. Patients with Gilbert's syndrome with elevated TBL may be enrolled as long as DBL, hemoglobin, and reticulocytes are normal.**

Reason for being an exclusion criterion	Asymptomatic, transient, dose-related transaminase elevations without associated increases in bilirubin were observed in the phase 2 fezolinetant program. Pre-existing conditions described in this exclusion criterion could have interfered with the assessment of hepatic safety in the clinical trials.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	Based on a review of the totality of data from the phase 2b and phase 3 program, the independent Liver Safety Monitoring Panel (LSMP) concluded that fezolinetant treatment at 45 mg/day is generally safe for the liver. In the phase 3 program, there were no Hy's Law cases and no serious liver injury as defined by international consensus criteria were observed. The ALT elevations > 3 x ULN were infrequently observed and occasionally accompanied by AST elevations. Out of 48 cases assessed by the LSMP (those with ALT or AST elevations >3 x ULN or TBL elevations >2 x ULN), 9 cases were assessed as probably related to study drug. No participant characteristics (BMI, history of NAFLD or NASH, age, race, concomitant medications, or race/ethnicity) clearly distinguished these 9 cases from others in the clinical trials. Transaminase elevations > 3x ULN were generally hepatocellular in nature, asymptomatic, occurred at points throughout the 52 weeks of exposure without overt patterns and typically resolved rapidly whether study drug treatment was continued or stopped. There was no dominant pattern of rise and fall of transaminase values. Based on the currently available clinical and post-marketing information, the MAH considers DILI, AST increased, and ALT increased to be an ADR for fezolinetant as described in the current SmPC of 2025. As the clinical trial program supports the overall hepatic safety of fezolinetant, DILI, ALT increased and AST increased described as an ADR in the SmPC, this exclusion criterion is not considered to be missing information.
Criterion 10	**Subject has creatinine > 1.5 × ULN; or estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula < 59 mL/min per 1.73 m^2 at screening.**
Reason for being an exclusion criterion	These subjects were excluded from the phase 3 studies because renal impairment could increase the exposure of fezolinetant and potentially confound the safety assessment.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	There were no clinically relevant changes in renal clinical chemistry parameters in the fezolinetant groups of the phase 3 studies. This is supported by results from phase 2b, phase 1 and nonclinical studies. There were no clinically meaningful changes over time, or changes from baseline in renal biochemistry parameters in the phase 2b study (study ESN364_HF_205).

	In the phase 1 renal impairment study (2693-CL-0008) that was conducted in parallel with the phase 3 studies, mild, moderate and severe renal impairment had marginal effects on pharmacokinetic exposure of fezolinetant. No relationship was found between renal function (eGFR) and pharmacokinetic parameters of fezolinetant. The pharmacokinetic exposure of the major metabolite of fezolinetant, ES259564 progressively increased with the severity of renal impairment as compared to respective normal renal function groups. There is no pharmacokinetic information in individuals with End-Stage Renal Disease. There are no robust data to support a clinical interpretation of the increase in metabolite exposure alone. Nonclinically, no histopathological changes were observed in the kidney in rats. Nephropathy was observed in 1 cynomolgus monkey, but this was thought to be caused by deteriorated conditions rather than an effect of fezolinetant. Based on the phase 1 renal impairment study (2693-CL-0008), the SmPC describes that fezolinetant is not recommended for use in individuals with severe (eGFR less than 30 mL/min/1.73 m^2) renal impairment. It also describes that fezolinetant has not been evaluated in individuals with end-stage renal disease (eGFR less than 15 mL/min/1.73 m^2) and is not recommended for use in this population. Because of the description in the SmPC and the absence of scientific rationale to suspect a different safety profile in the population described in the exclusion criterion, this exclusion criterion is not considered missing information.
Criterion 11	**Subject has a history of suicide attempt or suicidal behavior within the last 12 months or has suicidal ideation within the last 12 months (a response of "yes" to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale [C-SSRS]), or who is at significant risk to commit suicide, as assessed by the investigator at screening and at the time of visit 2 (randomization).**
Reason for being an exclusion criterion	Fezolinetant can cross the blood brain barrier. Pre-existing conditions related to suicide could have interfered with the assessment of efficacy and / or safety, specifically the evaluation of any effects on the C-SSRS, in clinical trials. In addition, a participant with such pre-existing condition has a higher risk of suicide; this exclusion criterion was set up to exclude study participants from that risk.
Is it considered to be included as missing information?	No
Rationale (if not included as missing information)	In the phase 3 program, there were no effects of fezolinetant on the CNS (with the possible exception of insomnia, which is considered an ADR). There was no effect on suicidal ideation or behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS).

	In addition, the incidence of the treatment-emergent AESI of depression was low and similar between placebo and fezolinetant groups with no dose relationship observed. This is supported by the results from the phase 2b study, where no clinically meaningful changes were observed regarding suicide status (study ESN364_HF_205). The data support the CNS safety of fezolinetant. There is no evidence of risk of de novo suicidal behavior or suicide in the clinical trial program. Because of the absence of scientific rationale to suspect a different safety profile in the population described in the exclusion criterion, this exclusion criterion is not considered missing information.

ADR: Adverse Drug reaction; AESI: Adverse Event of Special Interest; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AUC: Area Under Curve; BMI: Body Mass index; CI: Confidence Interval; CNS: Central Nervous System; CYP1A2: Cytochrome P450 1A2; DBL: Direct bilirubin ; DDI: Drug-Drug Interaction; DILI: Drug-Induced Liver Injury; EEG: Electroencephalogram; EMA: European Medicines Agency; FDA: Food and Drug Administration; eGFR: Estimated Glomerular Filtration Rate; HRT: Hormonal Replacement Therapy; INR: International Normalized Ratio; LSMP: Liver Safety Monitoring Panel, MAH: Marketing Authorization Holder; MRHD: Maximum Recommended Human Dose; NAFLD: Non Alcoholic Fatty Liver Disease; NASH: Nonalcoholic Steatohepatitis; NK3: Neurokinin 3; SmPC: Summary of Product Characteristics; SEER: Surveillance, Epidemiology, and End Results; SSRI: Selective Serotonin Reuptake Inhibitors; C-SSRS: Columbia Suicide Severity Rating Scale ; TBL: Total Bilirubin; TEAE: Treatment-Emergent Adverse Events; TVU: TransVaginal Ultrasound; ULN: Upper Limit of Normal; VMS: Vasomotor Symptoms

SIV.2 Limitations to detect adverse reactions in clinical trial development program

The VMS clinical development program for fezolinetant was unlikely to detect certain types of adverse reactions such as rare ≥ (1/10,000 to < 1/1,000) adverse reactions, adverse reactions with a long latency (> 1 year), or those caused by prolonged exposure (> 1 year).

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Table SIV.3: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program. This population is not considered missing information.
Breastfeeding women	Not included in the clinical development program. This population is not considered missing information.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Subjects with active liver disease or severe chronic hepatic impairment were not studied in the 2693-CL-0301, 2693-CL-0302, 2693-CL-0304, 2693-CL-0305, 2693-CL-0307, 2693-CL-0312 and 2693-CL-0206 clinical trials. In a dedicated phase 1 hepatic impairment study, the plasma AUC of fezolinetant increased with the severity of hepatic impairment (approximately 56% and 95% for mild and moderate hepatic impairment, respectively). There is no pharmacokinetic information in subjects with severe hepatic impairment (Child-Pugh Class C). The population with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment is considered missing information.
Patients with renal impairment	Subjects with moderate renal impairment (eGFR <60) were not studied in the 2693-CL-0301, 2693-CL-0302, 2693-CL-0304, 2693-CL-0305, 2693-CL-0307, 2693-CL-0206 and 2693-CL-0312 clinical trials. A dedicated phase 1 renal impairment study was performed. No relationship was found between renal function (eGFR) and pharmacokinetic parameters of fezolinetant. The pharmacokinetic exposure of metabolite ES259564 progressively increased with the severity of renal impairment as compared to respective normal renal function groups. There is no robust data to support a clinical interpretation of this 5-fold increase in metabolite exposure. There is no pharmacokinetic information in individuals with End-Stage Renal Disease. This population is not considered missing information.
Patients with cardiovascular impairment	Subjects with cardiovascular impairment were not included in the clinical development program. This population is not considered missing information.
Immunocompromised patients	Immunocompromised subjects were not included in the clinical development program. This population is not considered missing information.
Elderly population	Fezolinetant has not been evaluated for safety and efficacy in women initiating fezolinetant treatment over 65 years of age. This population is not considered missing information.

Type of special population	Exposure
Pediatric population	The Pediatric Committee agreed that fezolinetant for the adult indication falls under the scope of the Agency Decision CW/0001/2015 on class waivers because it is considered to belong to "all classes of medicinal products for treatment of climacteric symptoms associated with decreased estrogen levels, as occurring at menopause" (EMEA-18-2018). There is no relevant use of fezolinetant in the pediatric population. The safety and efficacy of fezolinetant in children under 18 years of age have not been established. No data are available. This is not considered missing information.
Population with relevant different ethnic origin	Subjects with different ethnic origins have been included in the development program as follows: White: 2246 subjects (1589.32 person years) Black/African American: 473 subjects (334.22 person years) Asian: 566 subjects (261.58 person years) Other: 26 subjects (18.17 person years)
Subpopulations carrying relevant genetic polymorphisms	Not applicable

AUC: Area Under the Curve; eGFR: Estimated Glomerular Filtration Rate; EMA (EMEA): European Medicines Agency

PART II: MODULE SV. POSTAUTHORIZATION EXPERIENCE

Data-lock point for this Module	11 Nov 2024
Version when Module last updated	4.0

SV.1 Post authorization exposure

SV.1.1 Method used to calculate exposure

The estimated patient exposure from marketing experience is based on internal company sales data. This estimate is based on standard units sold from 12 May 2023 (International birth date) to 11 Nov 2024. The market exposure has been calculated using data from available sales volume and assumes that on average 1 tablet sold accounts for 1 patient-day.

SV.1.2 Exposure

It is estimated that the cumulative exposure from 12 May 2023 up to the data lock point (DLP, 11 Nov 2024) is 58 326 patient-years.

PART II: MODULE SVI. ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Data-lock point for this Module	21 Jan 2022
Version when Module last updated	1.0

Potential for misuse for illegal purposes

There is no potential illegal misuse for fezolinetant. In both the nonclinical and clinical fezolinetant studies, there is no evidence for abuse liability potential.

PART II: MODULE SVII. IDENTIFIED AND POTENTIAL RISKS

Data-lock point for this Module	11 Nov 2024
Version when Module last updated	4.0

SVII.1 Identification of safety concerns in the initial Risk Management Plan submission

Following a review of the pooled phase 3 study data in the VMS development program, which included 3 studies in menopausal women comparing fezolinetant to placebo (2693-CL-0301, 2693-CL-0302 and 2693-CL-0304), no safety concerns were identified for inclusion in the risk management plan (RMP) as important identified risks or important potential risks.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Alanine aminotransferase (ALT) and/or Aspartate Aminotransferase (AST) increased

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

ALT and/or AST increased:

ALT elevations > 3 x Upper Limit of Normal (ULN), occasionally accompanied by AST elevations, were infrequently observed with fezolinetant treatment, but numerically greater in the fezolinetant 45 mg compared with placebo. ALT or AST elevations > 5 x ULN were infrequent and balanced across treatment groups. These elevations were generally transient and typically resolved on continued therapy or shortly after drug discontinuation. There was no discernable pattern of time to onset of transaminase elevations across the treatment groups and no dominant pattern of rise and fall of transaminase values. None of the transaminase elevations were accompanied by concomitant changes in elevated total bilirubin. No cases of Hy's law were reported in the fezolinetant clinical development program. The analyses in the hepatic safety evaluation were consistent with that observed in the background epidemiology for this population. Reported adverse event data for hepatic safety are concordant with the laboratory hepatic safety findings. Subgroup analysis by various intrinsic and extrinsic factors did not identify specific subpopulations at increased hepatic safety risk associated with fezolinetant treatment. More serious liver toxicity was not observed.

In the SmPC, section 4.4 describes that women with active liver disease of Child-Pugh Class B or C chronic hepatic impairment were not included in the clinical trials with fezolinetant; that elevations of ALT and/or AST > 3 x ULN occurred and that monitoring of liver transaminases in women with known or suspected hepatic disorder is advised during treatment. In addition, section 4.8 lists ALT increased, and AST increased as ADRs.

ALT increased and AST increased are not considered important risks, as these are not expected to have a clinically significant impact on the benefit-risk balance of fezolinetant

with the recommended dose of 45 mg once daily and routine pharmacovigilance and routine risk minimization activities are sufficient to manage these ADRs.

SVII.1.2 Risk considered important for inclusion in the list of safety concerns in the RMP

There are no risks considered important for inclusion in the RMP as safety concerns for fezolinetant.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

DILI is a new important identified risk in the list of safety concerns.

Reason for addition of the safety concerns: Based on PRAC recommendations dated 28 Nov 2024, DILI has been included a new important identified risk in the list of safety concerns.

Background:

The pooled phase 3 study data in the VMS development program included 3 studies in menopausal women comparing fezolinetant to placebo (2693-CL-0301, 2693-CL-0302, 2693-CL-0304).

In phase 3 clinical trials (2693-CL-0301, 2693-CL-0302, 2693-CL-0304) 52-week data population (POP2), elevations in serum ALT levels at least 3 times the ULN occurred in 2.1% of women receiving fezolinetant 45 mg compared with 0.8% of women receiving placebo. Elevations in serum AST levels at least 3 times the ULN occurred in 1.0% of women receiving fezolinetant 45 mg compared with 0.4% of women receiving placebo.

Studies completed after the initial RMP submission (2693-CL-0312, 2693-CL-0206, 2693-CL-0305 and 2693-CL-0307) also investigated hepatic safety and evaluated ALT and AST.

In study 2693-CL-0312, the proportion of participants with ALT > 3 x ULN in the 24-week data was 0 in the placebo group and 1.3% in the fezolinetant 45 mg group, and none with AST > 3 x ULN in both placebo and fezolinetant 45 mg groups.

In study 2693-CL-0305, the proportion of participants with ALT >3 x ULN or AST > 3 x ULN after 12-weeks of treatment was 0.7% in the placebo group and 0 in the fezolinetant 30 mg group.

In study 2693-CL-0307, the proportion of participants with ALT >3 x ULN or AST > 3 x ULN after 52-weeks of treatment was 1.4% in the fezolinetant 30 mg group.

In study 2693-CL-0206, the proportion of participants with ALT >3 x ULN or AST > 3 x ULN after 12-weeks of treatment was 0 in the placebo group, 0 in the fezolinetant 15 mg group, and 2.1% in the fezolinetant 30 mg group.

Given the different designs and fezolinetant doses studied in the clinical studies completed after the initial RMP submission, it is not appropriate to pool the data of ALT and AST

increases with the 52-week data from the POP2 from the global phase 3 studies, Therefore, it is not possible to recalculate the frequency of the ADRs ALT increased and AST increased.

In the postmarketing setting, serious but reversible hepatic laboratory test abnormalities have been observed. Patients experienced transaminase elevations (more than 10 times the ULN) concurrent with elevations in bilirubin and/or alkaline phosphatase (ALP), sometimes associated with signs or symptoms such as fatigue, pruritus, jaundice, dark urine, or abdominal pain.

Risk-benefit impact:

Events of ALT increased and AST increased observed in fezolinetant-treated patients during clinical trial use resolved after drug discontinuation. These transaminase elevations were rarely associated with clinical symptoms. None of the events progressed serious liver dysfunction, cirrhosis or led to death.

The serious hepatic laboratory test abnormalities and adverse event reports of DILI have been observed in post-marketing reports. In instances where outcome data was available, these adverse events have been reversible after discontinuation of treatment. The overall impact on the benefit-risk balance of the product is estimated to be low considering the risk mitigation: description of the risk in the SmPC, providing guidance on when not to start treatment with fezolinetant, guidance for evaluation of hepatic function during treatment and guidance for when to discontinue treatment with fezolinetant in case of transaminase increases and /or clinical signs and symptoms of hepatic dysfunction.

Overall, the benefits of fezolinetant outweigh the risks in the treatment of VMS associated with menopause.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII3.1 Presentation of important identified risks and important potential risks

Important Identified Risk: DILI

Potential mechanisms: The mechanism by which fezolinetant might cause DILI is unclear.

Evidence source(s) and strength of evidence: This important identified risk is based on safety data observed in the clinical development program and accumulated post-marketing reports of patients experiencing transaminase elevations of more than 10 times the ULN concurrent with elevations in bilirubin and/or ALP, sometimes associated with signs or symptoms such as fatigue, pruritus, jaundice, dark urine, or abdominal pain.

Characterization of the risk:

These findings are aligned with the data from study 2693-CL-0304 (POP4) data, a subset of POP2, which showed that ALT > 3 x ULN was observed in 0.9% of participants in the placebo group, 1.2% in the fezolinetant 30 mg group and 1.9% in the fezolinetant 45 mg group. Overall, these data show a pattern of increased ALT > 3 x ULN in fezolinetant-treated participants compared with placebo based on the laboratory data, with a higher incidence in the fezolinetant 45 mg group.

The proportion of participants with AST > 3 x ULN in the 52-week POP2 data was 0.4% in the placebo group, 0.8% in the total fezolinetant 30 mg group, and 1.0% in the total fezolinetant 45 mg group. These findings are aligned with the POP4 data, which showed that AST > 3 x ULN was observed in 0.5% of participants in the placebo group, 0.8% in the fezolinetant 30 mg group, and 0.8% in the fezolinetant 45 mg. Overall, there was no appreciable difference regarding AST elevations > 3 x ULN between the treatment arms.

Exposure-adjusted incidence rates for AST or ALT elevations to > 3 x ULN were 1.5 and 2.3 per 100 participant-years for placebo and total fezolinetant, respectively in POP2. The observed exposure-adjusted incidence rate was 1.8 per 100 participant-years for the fezolinetant 30 mg total group and 2.7 per 100 participant-years for the fezolinetant 45 mg total group. Exposure-adjusted incidence rates for elevations > 5 x ULN were balanced between treatment groups and elevations > 8 x ULN were rare (0.1% in the total fezolinetant group).

In the latest completed study 2693-CL-0312, the proportion of participants with ALT > 3 x ULN in the 24-week data was 0 in the placebo group and 1.3% in the fezolinetant 45 mg group, and none with AST > 3 x ULN in both placebo and fezolinetant 45 mg groups.

The onset of transaminase elevations occurred at various time points throughout the study durations, and there was no overt cluster of time to onset across the treatment groups, and there was no dominant pattern of rise and fall of the transaminase values. Liver enzyme elevations were typically reversible and asymptomatic and generally resolved while on treatment or after treatment discontinuation.

In the post-marketing setting, until 11 Nov 2024, 194 cases[1] (all valid and invalid cases) were received reporting hepatic events, including liver abnormalities. Twenty-six cases were serious based on the reported event and/or extent of elevation of transaminase (>5x ULN) [CIOMS, 2020]. The majority of cases consisted of non-serious hepatic events (n=168) with asymptomatic transaminases increased, without concurrent alkaline phosphatase and/or total bilirubin elevations. The majority of liver abnormalities were reported in the first 3 months and declined thereafter, with no events reported after 9 months of exposure. Three cases included liver abnormalities showing concurrent increases of transaminase > 3x ULN and total bilirubin >2x ULN. Importantly, when the outcome was reported, liver test abnormalities consistently normalized after discontinuation of fezolinetant (15%). Additional signs or symptoms were noted in 18 out of 194 cases, including 7 out of 26 serious cases that warranted laboratory tests. However, the timing of these symptoms in relation to liver test abnormalities was frequently ambiguous because of limited available data. Based on the totality of data related to hepatic enzyme increases, with some serious cases of concurrent increases in total bilirubin and cases with signs or symptoms suggesting DILI, the risk has been identified and characterized as “DILI”.

[1] SMQ: Drug related hepatic disorders- comprehensive search (Broad)

Risk factors and risk groups:

Common risk factors for DILI include non-alcoholic fatty liver disease (NAFLD), non–alcoholic steatohepatitis (NASH), heavy alcohol intake, use of some medications, illegal drug use, metabolic syndrome, obesity, diabetes and dyslipidemia [Sheka et al, 2020; Pratt & Kaplan, 2000]. The global increased incidence of NAFLD has increased with the increasing prevalence of obesity, type 2 diabetes, and metabolic syndrome [Sheka et al, 2020; Thandra et al, 2020; Perumpail et al, 2017; Rinella, 2015; Vernon et al, 2011].

Preventability:

In addition to known risk factors and risk groups for DILI, hepatic function (ALT, AST, ALP, and bilirubin) should be evaluated before initiating therapy.

The inclusion of guidance on when not to initiate fezolinetant can prevent serious outcomes and will ensure that the patients initiating fezolinetant will have a normal hepatic function.

Recommendations on monthly follow-up evaluation of hepatic function for the first 3 months after the start of treatment allow to determine early transaminase elevations and allow the healthcare professionals (HCP) and patient to make decisions on continuation or discontinuation of treatment. Additional follow-up evaluation thereafter, based on clinical judgement, allows to determine transaminase elevations before patients potentially become symptomatic thereby preventing serious outcomes.

Additionally, raising awareness of signs and symptoms of DILI and language to discontinue immediately and seek medical attention if symptoms might suggest DILI in the SmPC will inform patients and HCPs of which symptoms to be cognizant of. Discontinuation of treatment upon experiencing symptoms has been shown to resolve the symptoms.

Impact on the risk-benefit balance of the product:

Events of ALT and AST increases observed in fezolinetant-treated patients during clinical trial use resolved after drug discontinuation. These transaminase elevations were rarely associated with clinical symptoms. None of the events progressed to serious liver injury or led to death.

The serious hepatic laboratory test abnormalities and adverse event reports of DILI seen post-marketing have been reversible after discontinuation of treatment. The overall impact on the risk-benefit balance of the product is estimated to be low considering the implemented risk mitigation measures, including a description of the risk in the SmPC, providing guidance on when not to start treatment with fezolinetant, guidance for evaluation of hepatic function during treatment and guidance for when to discontinue treatment with fezolinetant in case of transaminase increases and /or clinical signs of hepatic dysfunction.

Overall, the benefits of fezolinetant outweigh the risks in the treatment of VMS associated with menopause.

Public health impact:

DILI can cause serious health problems and result in liver failure. The impact on public health of this risk will be reduced with adequate risk communication to prescribers and patients in the label, which includes the importance of monitoring patients for hepatic function, guidance for discontinuation of fezolinetant and early detection by patients of potential DILI by identifying key signs and symptoms.

SVII.3.2 Presentation of the missing information

Missing information: Use in individuals with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment.

Evidence Source

Patients with chronic hepatic impairment [Child-Pugh Class B (moderate) or C (severe)] starting treatment for moderate to severe VMS may be at increased risk. A potential different safety profile in this particular subpopulation is anticipated based on phase 1 data (2693-CL-0007). In a dedicated phase 1 hepatic impairment study, the plasma area under the curve (AUC) of fezolinetant increased with severity of hepatic impairment (approximately 56% and 95% for mild and moderate hepatic impairment, respectively). There is no pharmacokinetic information in subjects with severe hepatic impairment (Child-Pugh Class C). In phase 3, women with severe chronic hepatic impairment were excluded from the clinical trials.

The SmPC sections 4.2 and 4.4 describe that fezolinetant is not recommended for use in individuals with Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment. Fezolinetant has not been studied in individuals with Child-Pugh Class C (severe) chronic hepatic impairment.

Continued monitoring for anticipated risks reported in moderate or severe chronic hepatic impairment will occur through routine pharmacovigilance measures.

PART II: MODULE SVIII. SUMMARY OF THE SAFETY CONCERNS

Data-lock point for this Module	11 Nov 2024
Version when Module last updated	4.0

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• DILI
Important potential risks	• None
Missing information	• Use in individuals with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment.

DILI: Drug-Induced Liver Injury

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

Data-lock point for this Module	11 Nov 2024
Version when Module last updated	4.3

III.1 Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection

To further identify and characterize the important identified risk of "DILI", as well as missing information "Use in individuals with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment", Astellas will use a specific standardized adverse drug reaction follow-up questionnaire.

Specific adverse reaction follow-up questionnaire for DILI and Use in individuals with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment:

Description	Purpose	Safety concern(s) addressed
Fezolinetant Follow-up Questionnaire for Hepatic Adverse Events	This follow-up questionnaire, as part of routine pharmacovigilance activities beyond spontaneous adverse event reporting and signal detection will be sent to the health care professionals for each hepatic adverse event reported. In case fezolinetant was incidentally used by a patient with Child-Pugh B or C hepatic impairment, this questionnaire will serve as a way to identify and characterize the use in this population.	DILI (Important identified risk) Use in individuals with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment (Missing information)

The adverse event follow-up questionnaire is provided in [Annex 4].

DILI: Drug-Induced Liver Injury

III.2 Additional pharmacovigilance activities

Pending results from a feasibility assessment, a NI-PASS is proposed for evaluating the effectiveness of fezolinetant RMMs in targeted European countries using secondary use data sources.

The proportion of patients following recommended hepatic laboratory test monitoring, both prior to initiation and during fezolinetant treatment, starting after implementation of the updated RMMs, will be evaluated. Further, the proportion of patients with abnormal test results among those who were tested and initiated treatment will be evaluated. Finally, the proportion of patients who should have stopped treatment after abnormal testing results (but did not) will also be evaluated.

This study aims to evaluate whether updated RMMs have been effective by assessing the practice of hepatic laboratory testing ordered by HCPs and their prescription behavior after abnormal test results. This is to assess HCPs' adherence to the recommendations for hepatic laboratory testing prior to initiation of as well as during treatment, and adherence to the recommendations not to initiate and to stop treatment after abnormal test results.

An updated version of the study synopsis, as well as the proposal of the feasibility assessment to be conducted for the main study, are included in Annex 3 Part A.

In the case that the feasibility assessment for a multi-database study based on secondary use data sources does not confirm that such an approach is feasible, then an alternative study design will be proposed to evaluate the effectiveness of the RMMs.

III.3 Summary table of additional pharmacovigilance activities

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
NI-PASS for effectiveness evaluation of RMMs	To evaluate whether updated RMMs are effective by assessing the practice of hepatic laboratory testing ordered by HCPs and the prescribing behavior after abnormal test results.	DILI	Feasibility assessment Report and NI-PASS protocol submission to EMA	Planned for: 4Q2026
			Protocol approval by EMA	2Q2027
			Data collection completion	4Q2028
			Data analysis completion	1Q2029
			Study report submission to EMA	2Q2029

DILI: Drug-Induced Liver Injury; EMA: European Medicines Agency; HCPs: Healthcare Professionals; NI-PASS: Non-Interventional Post-Authorization Safety Study; RMM: Risk Minimization Measure.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Data-lock point for this Module	21 Jan 2022
Version when Module last updated	1.0

Table Part IV.1: Planned and ongoing postauthorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorization				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

Data-lock point for this Module	11 Nov 2024
Version when Module last updated	4.2

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
DILI	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Section 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations for liver function monitoring, when not to start and when to discontinue treatment with fezolinetant are included in SmPC section 4.4 and in PL section 2 DHPC has been implemented as a routine RMM.
Use in individuals with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment.	Routine risk communication: • SmPC Sections 4.2 and 4.4 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations not to use fezolinetant in patients with Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment are provided in SmPC sections 4.2 and 4.4 as well as in PL section 2.

DHPC: Direct Healthcare Professional Communication; DILI: Drug-Induced Liver Injury; PL: Package Leaflet; RMM: Risk Minimization Measure; SmPC: Summary of Product Characteristics

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.2.1 Removal of additional risk minimization activities

DHPC has been removed as an additional RMM and included as routine RMM.

Rationale for the removal: DHPC has been removed as an additional RMM to be in alignment with GVP Modul XVI, Rev. 3.

V.3 Summary of Risk Minimization Measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
DILI	Routine risk communication: • SmPC Section 4.4 where recommendations are given on monitoring the liver function, when not to start and when to discontinue treatment with fezolinetant, and 4.8. • PL Section 2 where advice is given for liver function monitoring and to consult doctor if signs or symptoms of a liver problem occur, and 4. DHPC has been implemented as a routine RMM. Additional risk minimization measures: • None	Routine pharmacovigilance activities: • Adverse reaction reporting • Signal detection • Follow-up questionnaire for hepatic adverse events Additional pharmacovigilance activities: • NI-PASS to evaluate the effectiveness of the RMMs
Use in individuals with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment.	Routine risk communication: • SmPC Sections 4.2 and 4.4 where Recommendations are provided not to use fezolinetant in patients with Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment is provided • PL Section 2 Additional risk minimization measures: • None	Routine pharmacovigilance activities: • Adverse reaction reporting • Signal detection • Follow-up questionnaire for hepatic adverse events Additional pharmacovigilance activities: • None

DHPC: Direct Healthcare Professional Communication; DILI: Drug-Induced Liver Injury; NI-PASS: Non-interventional Post-Authorization Safety Study; PL: Package Leaflet; RMM: Risk Minimization Measure; SmPC: Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

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Summary of risk management plan for VEOZA (fezolinetant)

This is a summary of the risk management plan (RMP) for VEOZA. The RMP details important risks of VEOZA, how these risks can be minimized, and how more information will be obtained about VEOZA's risks and uncertainties (missing information).

The VEOZA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how VEOZA should be used.

This summary of the RMP for VEOZA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of the VEOZA's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

VEOZA 45 mg tablets are authorized for the treatment of moderate to severe VMS associated with menopause. It contains fezolinetant as an active substance and it is given by oral route as 45 mg film-coated tablet.

Further information about the evaluation of VEOZA's benefits can be found VEOZA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page >.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of VEOZA, together with measures to minimize such risks and the proposed studies for learning more about the risks of VEOZA, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, are in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without a prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary.

These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of VEOZA is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of VEOZA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential.

- Identified risks are concerns for which there is sufficient proof of a link with the use of VEOZA.
- Potential risks are concerns for which an association with the use of VEOZA is possible based on available data, but this association has not been established yet and needs further evaluation.
- Missing information refers to information on the safety of VEOZA that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• DILI
Important potential risks	• None
Missing information	• Use in individuals with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment

DILI: Drug-Induced Liver Injury

II.B Summary of important risks

Important identified risk: DILI

Evidence for linking the risk to the medicine	This important identified risk is based on data from the safety population in the clinical development program and patients treated in the post-marketing setting.
Risk factors and risk groups	Common risk factors for DILI include NAFLD, NASH, heavy alcohol intake, use of some medications, illegal drug use, metabolic syndrome, obesity, diabetes and dyslipidemia [Sheka et al, 2020; Pratt & Kaplan, 2000]. The global increased incidence of NAFLD has increased with increasing prevalence of obesity, type 2 diabetes and metabolic syndrome [Sheka et al, 2020; Thandra et al, 2020; Perumpail et al, 2017; Rinella, 2015; Vernon et al, 2011].
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where recommendations are given on monitoring the liver function, when not to start and when to discontinue treatment with fezolinetant, and 4.8.

	• PL Section 2 where advice is given for liver function monitoring and to consult doctor if signs or symptoms of a liver problem occur, and 4 DHPC has been implemented as a routine RMM. Additional risk minimization measure • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • An NI-PASS to evaluate the effectiveness of the RMMs

DHPC: Direct Healthcare Professional Communication; DILI: Drug-Induced Liver Injury; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-alcoholic steatohepatitis; NI-PASS: Non-Interventional Post-Authorization Safety Study; PL: Package Leaflet; RMM: Risk Minimization Measure; SmPC: Summary of Product Characteristics

Missing information: Use in individuals with Child-Pugh Class B or C (moderate or severe) chronic hepatic impairment

Risk minimization measures	Routine risk communication: • SmPC Sections 4.2 and 4.4 where recommendations are provided not to use fezolinetant in patients with Child-Pugh Class B (moderate) or C (severe) chronic hepatic impairment • PL Section 2 Additional risk minimization measure • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

PL: Package Leaflet; SmPC: Summary of Product Characteristics

II.C Postauthorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of marketing authorization or specific obligation for fezolinetant.

II.C.2 Other studies in postauthorization development plan

Study short name: NI-PASS for effectiveness evaluation of RMMs

Purpose of the study: This study aims to evaluate whether updated RMMs are effective by assessing the practice of hepatic laboratory testing ordered by HCPs and the prescribing behavior after abnormal test results**.** This is to assess HCPs' adherence to the recommendations for hepatic laboratory testing prior to initiation of as well as during treatment, and adherence to the recommendations not to initiate and to stop treatment after abnormal test results.

PART VII: ANNEXES

Table of Contents

Annex 4 - Specific adverse event follow-up forms

Data-lock point for this annex	11 Nov 2024
Version when annex last updated	4.0

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Follow-up forms: Fezolinetant Follow-up Questionnaire for Hepatic Adverse Events

Case Number:				
Reported Event:		**Patient Details:**	Age/Age group	☐ Male ☐ Female

Thank you for reporting the initial report related to Hepatic Adverse Event(s) during the use of Fezolinetant. With this questionnaire, we would like to request specific follow-up information, in order to perform a better scientific evaluation of the case. Please tick all relevant grey boxes below.

SIGNS AND SYMPTOMS OF THE EVENT		
☐ None	☐ Hepatic encephalopathy	☐ Nausea/vomiting
☐ Abdominal pain	☐ Hypochondrium pain right	☐ Pruritus
☐ Ascites	☐ Jaundice	☐ Rash
☐ Asterixis	☐ Lack of appetite	☐ Splenomegaly
☐ Change in color of stool/urine	☐ Liver atrophy	☐ Urticaria
☐ Epigastric pain	☐ Liver enlargement	☐ Other:
☐ Hematemesis	☐ Malaise	
☐ Hepatic coma	☐ Marked weight loss	

UNDERLYING CONDITIONS / RISK FACTORS	
☐ Alcohol use (units per week):	☐ Other liver disease:
☐ Alcoholic hepatitis:	☐ Pneumonia:
☐ Abdominal surgery, related to hepatobiliary system:	☐ Prior exposure to chemicals or toxins:
☐ Allergic reaction:	
☐ Autoimmune disease:	☐ Recent exposure to blood products/plasma, fraction product or transfusion:
☐ Biliary stricture/ Bilestones/Biliary disease, other:	☐ Renal disease, specify type and/or stage if chronic:
☐ Cardiac disorders-including right heart failure or hypotension:	☐ Recent tattoos:
☐ Cirrhosis:	☐ Recent travel:
☐ Connective tissue disease:	☐ Sepsis:
☐ Diabetes mellitus:	☐ Supplement/ Food types (e.g., weight loss product, green juice, agaricus, Glucosamine)/Herbal preparations (e.g., Turmeric):
☐ Drug Abuse:	
☐ Dyslipidemia:	
☐ Fatty liver / steatohepatitis:	☐ Similar reactions in the past:
☐ Family history of liver disease:	☐ Unusual intense physical exercise:

☐ Primary liver cancer/Hepatic metastases:	☐ Viral illness:
☐ Genetic disease (e.g., Alpha 1 antitrypsin deficiency):	☐ Possible drug interaction:
☐ Hemodynamic instability, shock:	☐ Smoking (packs per week):
☐ Infectious Hepatitis (including HAV, HBV, HCV, HDV, HEV, CMV or EBV): ☐ past ☐ current	☐ Other:
☐ Neutropenic infections:	☐ None

FEZOLINETANT AND CONCOMITANT MEDICATIONS

DRUG NAME	SUSPECT PRODUCT (S) CONCOMITANT (C)	INDICATION	DOSE/FREQUENCY/ ROUTE OF ADMINISTRATION	START DATE dd-Mmm-yyyy	STOP DATE dd-Mmm-yyyy or Ongoing
☐ Fezolinetant					
☐					
☐					

DECHALLENGE AND RECHALLENGE INFORMATION

Did the hepatic adverse event(s) subside or disappear upon removal of fezolinetant?:
Did the hepatic adverse event(s) reappear when fezolinetant was restarted?:

HEPATIC ADVERSE EVENT OUTCOME

☐ Liver transplant	☐ Not resolved	☐ Unknown
☐ Lost to follow-up	☐ Resolved with or without sequelae	☐ Other:

SERIOUSNESS OF HEPATIC ADVERSE EVENT *Did the adverse event(s) result in any of the following type of outcome(s)?*

☐ Death	☐ Persistent or significant disability/incapacity
☐ Life-threatening	☐ Congenital anomaly/birth defect
☐ Inpatient hospitalization	☐ Other serious or important medical event:
☐ Prolongation of existing hospitalization	

CAUSALITY ASSESSMENT *(between Fezolinetant and the Hepatic Adverse Event)*

☐ Related	☐ Not Related

TIME FROM FEZOLINETANT INITIATION TO OCCURRENCE OF THE HEPATIC ADVERSE EVENT(S)

HEPATIC ADVERSE EVENT	TIME FROM FEZOLINETANT INITIATION TO OCCURRENCE OF THE ADVERSE EVENT

TREATMENT FOR HEPATIC ADVERSE EVENT(S)

DRUG/TREATMENT NAME	DOSE/FREQUENCY/ ROUTE OF ADMINISTRATION	START DATE dd-Mmm-yyyy	STOP DATE *dd-Mmm-yyyy* or *Ongoing*

RELEVANT INVESTIGATIONS *Provide results at time of the event. Provide other results (baseline, peak of event and resolution) in Additional Details field or attach as copy.*		
INVESTIGATION	**DATE** dd-Mmm-yyyy	**RESULT/UNIT**
☐ Alanine transaminase (ALT)		
☐ Alkaline Phosphate (ALP)		
☐ Alpha fetoprotein		
☐ Ammonia		
☐ Aspartate transaminase (AST)		
☐ Autoantibodies for Immunologic diseases (e.g., AMA, ANA, ANCA or ASMA):		
☐ Bilirubin (specify type):		
☐ Total Bilirubin		
☐ Drug Screening Tests:		
☐ Eosinophil Count		
☐ Gamma glutamyltransferase (γGT)		
☐ Immunoglobulins: ☐ Ig ☐ IgG ☐ IgM ☐ IgA		
☐ Lactate dehydrogenase (LDH)		
☐ Prothrombin time / International normalized ratio (PT / INR)		
☐ APTT, D-Dimer, and fibrin degradation product level:		
☐ Serum albumin		
☐ Serum free copper		
☐ Viral Serology (e.g., Ab, Ag, DNA for Hepatitis virus, EBV or CMV):		
☐ CT scan		
☐ Echography		
☐ Endoscopic ultrasound		
☐ ERCP (Endoscopic Retrograde Cholangiopancreatography)		

☐ Liver biopsy		
☐ Fezolinetant plasma levels		
☐ MRCP (Magnetic Resonance Cholangiopancreatography)		
☐ MRI (Magnetic Resonance Imaging)		
☐ Other:		

ADDITIONAL DETAILS / OTHER RELEVANT INFORMATION

REPORTER INFORMATION			
REPORTER NAME / CREDENTIALS	**REPORTER'S SPECIALTY**	**DATE** (dd-Mmm-yyyy)	**SIGNATURE** (to confirm the accuracy of the data)

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Data-lock point for this annex	11 Nov 2024
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Not applicable

Annex 7 - Other supporting data (including referenced material)

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